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Depression and Anxiety Disorders in COVID-19 Survivors: Role of Inflammatory Predictors

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ABSTRACT

Introduction: Infection-triggered perturbation of the immune system, which was observed after previous coronavirus outbreaks, could induce psychiatric sequelae. The spreading of the Coronavirus-19 (COVID-19) pandemic could be associated with psychiatric implications. In this study, we aimed to evaluate the association between inflammatory biomarkers and the levels of depression and anxiety in patients who recovered from COVID-19.

Methods: We screened 109 COVID-19 survivor adults for psychiatric symptoms on the 15th day of follow-up after discharge from the hospital. The patients were split into two groups, the ones with depression and anxiety, and the ones without depression or anxiety, after the psychiatric interview. Self-rating Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were applied to assess the levels in patients with depression and anxiety. We collected and recorded the sociodemographic information, clinical data, and baseline inflammatory markers.

Results: Higher baseline neutrophil/lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) were found in patients with depression and anxiety. Higher levels of depression and anxiety were found in younger and female patients. Besides, a significant correlation was found between BAI and ferritin levels in patients with anxiety, while no association was found between BAI and other inflammatory biomarkers. Moreover, no significant relationship was found between BDI scores and inflammatory biomarkers in patients with depression.

Conclusion: COVID-19 primarily affects the respiratory and cardiovascular systems. Nonetheless, psychiatric involvement is not uncommon and can lead to severe problems if not detected and managed at an early stage. It is recommended that clinicians should be vigilant in terms of psychiatric involvement in COVID-19 patients presenting with high inflammatory parameters.

Keywords: Anxiety, COVID-19, depression, inflammation

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INTRODUCTION

A novel coronavirus causing severe respiratory failure was first detected in China in December 2019 and called as COVID-19. Then this new disease spread to more than 200 countries and was announced as a "pandemic" by WHO (1). It caused 51 million cases and 1.2 million deaths worldwide until today. In the meantime, 397000 cases and 11000 deaths were reported in Turkey (2).

The disease caused by COVID-19 primarily involves respiratory, immune, and cardiovascular systems. However, central nervous system (CNS) involvements were also reported (3). Several hypotheses related to the pathophysiology of neurological system involvement in COVID-19 have been reported so far, while the exact mechanism is still unknown. According to most accepted hypotheses, COVID-19 can trigger CNS sequelae via direct viral spreading to CNS, or indirectly through an immune system response (4). Clinical, postmortem, animal, in vitro, and cell culture studies showed that coronaviruses have potential neurotrophic effects (5).

Highlights

- **The relationship between biomarkers, depression and anxiety in COVID-19 was evaluated.**
- **A higher N/L ratio and SII were found in patients with depression and anxiety.**
- **High inflammatory parameters are important for psychiatric involvement in COVID-19.**

Psychiatric problems related to COVID-19 have been reported so far. Social isolation, and quarantine (6–7), unexpected deaths of relatives (8), the stress on healthcare workers, and other employees (9), and economic troubles (10) have been reported as the reasons for the increased incidence

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of psychiatric problems such as anxiety, and depression due to COVID-19 pandemic. Nevertheless, it was reported that neuroinflammation, and cytokine storm secondary to immune response following the invasion of coronaviruses could cause psychiatric symptoms (11). In this study, we aimed to evaluate the association between inflammatory biomarkers and the levels of depression and anxiety in COVID-19 survivors.

METHODS

Ethics Committee of Sakarya Training and Research Hospital was approved for the study (Date: 11.09.2021, Number: 01-24T14-5036). Informed consent from all the participants were obtained.

Participants

This study was conducted between November 2020 and January 2021 at Sakarya University Training and Research Hospital which was assigned as a pandemic hospital by the Ministry of Health. We included 109 patients who were diagnosed with COVID-19 according to WHO guidelines, and discharged with full recovery after the treatment in the hospital. Then, psychiatric interviews were conducted with these patients. Forty-two patients were excluded out of 151 patients according to exclusion criteria. Exclusion criteria were the following: having a history of psychiatric disorder, undergoing treatment due to an active psychiatric disorder, being under the age of 18, having an impaired consciousness, delirium, and severe respiratory symptoms, having a (-) PCR test, being unwilling to attend the study.

Data Collection and Study Design

Sociodemographic attributes including age, gender, history of chronic illnesses, and history of psychiatric disorders of the patients who were admitted to the hospital with a positive COVID-19 PCR test were collected, and recorded. Sedimentation, white blood cell, lymphocyte, C-reactive Protein (CRP), neutrophil/lymphocyte ratio (NLR), systemic immune-inflammation index (SII) (SII=platelets X neutrophils/lymphocytes), procalcitonin, fibrinogen, lactate dehydrogenase (LDH), baseline inflammatory markers, and D – Dimer levels of all patients were recorded by using hospital medical files. All patients were evaluated for depression and anxiety by a psychiatric interview performed at least 15 days after discharge from the hospital. The patients were split into two groups, the ones with depression and anxiety, and the ones without depression or anxiety, after the psychiatric interview. Self-rating BDI, and BAI were applied to assess the levels of depression and anxiety.

Beck Depression Inventory (BDI): It was developed by Beck et al. (12). The inventory consists of 21 items. Each item is rated between 0 and 3, and its Turkish validity and reliability study was conducted (13). The cutoff value of inventory was specified as 17. Total collectable points from the inventory are between 0 and 63.

Beck Anxiety Inventory (BAI): It was developed by Beck et al. (14). It consists of 21 items. Each item is rated between 0 and 3, and its Turkish validity and reliability study was conducted (15).

Statistical Analysis

Mean value and standard deviation for parametric quantitative values, median, minimum, and maximum values for non-parametric used. Qualitative values are given as numbers and percentages. Shapiro-Wilk was used for normallity testing. For comparison of qualitative values Chi-square test was used, for comparison of quantitative values according to normality distribution Mann-Whitney U and T tests were used. For statistical significance $p<0.05$ was accepted. Analyses were performed using Statistical Package for the Social Sciences (SPSS) statistical software (IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp.)

RESULTS

Of 109 patients included in the study, 38 patients were diagnosed with depression (35%), and 71 patients had no sign of depression (65%). The median score of BDI was 32 (minimum-maximum: 27–38) in the patient group with depression. The median age of the group without depression was 65 (minimum-maximum: 56–75), while the median age of the group with depression was 53.5 (minimum-maximum: 39–63). The patient group with depression was significantly younger than the group without depression ($p<0.001$). Of all patients with COVID-19, 40 female patients (56%) had depression, and 13 female patients (34%) had no depression. Female patients had a significantly higher incidence of depression as compared with male patients ($p=0.028$).

Twenty-seven patients (25%) were diagnosed with anxiety disorder, and 82 patients (75%) had no sign of anxiety. The median BAI score was found as 34.5 (minimum-maximum: 26–41) in patients with anxiety. The median age of the group without anxiety was 65 (minimum-maximum: 55–75), while the median age of the group with anxiety was 52 (minimum-maximum: 38–62). The patient group with anxiety was significantly younger than the group without depression ($p<0.001$). Of all patients with COVID-19, 41 female patients (50%) had anxiety, and 12 female patients (41%) had no anxiety. Female patients had a significantly higher incidence of anxiety compared with male patients ($p=0.016$).

Among lab tests, lymphocyte counts, D-Dimer, ferritin, sedimentation, CRP, fibrinogen, and LDH levels were significantly higher in the group with depression as compared with the group without depression ($p=0.007$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.012$ respectively). The mean NLR was 6.1 (minimum-maximum: 4.4–10.2) in patients without depression, whereas it was 8.2 (minimum-maximum: 5.1–14.9) in patients with depression, and this difference was statistically significant ($p=0.047$). The mean SII score was 1368 (minimum-maximum: 733–2486) in the group without depression, while it was 2014 (minimum-maximum: 1204–3123) in the group with depression, and this difference was also significant ($p=0.032$).

When the lab parameters of the group with anxiety were analyzed, it was found that lymphocyte counts, D-Dimer, ferritin, sedimentation, CRP, fibrinogen, and LDH levels were significantly higher as compared with the group without anxiety ($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.008$ respectively). The mean NLR was 5.8 (minimum-maximum: 4.1–12) in patients without anxiety, while it was 9.1 (minimum-maximum: 6.8–14.9) in patients with anxiety, and this difference was statistically significant ($p=0.003$). The mean SII score was 1389 (minimum-maximum: 731–2331) in the group without anxiety, while it was 2495 (minimum-maximum: 1348–3172) in the group with anxiety, which means this difference was also significant ($p=0.002$). Sociodemographic attributes and the inflammatory parameters of the patients with and without depression or anxiety are compared in Table 1.

No significant association was determined between inflammatory parameters and BDI scores in patients with depression. There was also no correlation between BAI scores and inflammatory lab tests in patients with anxiety except for the moderate positive correlation between BDI and ferritin levels ($r=0.24$, $p=0.035$). Correlation levels between BAI, BDI scores, and inflammatory markers are shown in Table 2.

DISCUSSION

Higher baseline NLR and SII scores were found in patients with depression and anxiety as compared with patients without depression and anxiety. Besides, depression and anxiety levels were higher in female and younger patients. In addition to this, BAI scores were associated with ferritin levels, while no significant relationship was found between BAI scores and other

Table 1. Association of the patients with and without depression, and anxiety with sociodemogrophic attributes and inflammatory

	With depression symptoms (n=71)	Without depression symptoms (n=38)	p	With anxiety symptoms (n=82)	Without anxiety symptoms (n=27)	Total (n=109)	p
Age, median (range)	65 (56-75)	53.5 (39-63)	<0.001*	65 (55-75)	52 (38-62)	63 (52-72)	<0.001*
Gender, n (%)							
Female	40 (56)	13 (34)	0.028*	41 (50)	12 (44)	53 (49)	0.016*
Male	25 (66)	31 (44)		15 (56)	41 (50)	56 (51)	
WBC, median (range)	6.7 (5.4-10.5)	7.3 (5.2-11.3)	0.682	7 (5.1-10.6)	7.1 (5.4-11.3)	7 (5.4-11.2)	0.790
Neutrophil, median (range)	5.6 (3.8-7.1)	6 (3.8-9.5)	0.451	6 (4.1-7.4)	6 (3.7-9.4)	6 (3.8-8.4)	0.752
Lymphocyte, median (range)	0.8 (0.4-1)	0.9 (0.6-1.5)	0.007*	0.7 (0.4-0.9)	0.9 (0.6-1.5)	0.9 (0.6-1.3)	0.001*
Platelet, median (range)	215.5 (190-264)	201 (163-278)	0.358	240 (192-264)	202.5 (161-278)	208 (175-269)	0.179
D-Dimer, median (range)	194 (152-599)	549 (297-1150)	0.001*	187 (145-199)	588.5 (297-1280)	431 (193-984)	<0.001*
Ferritin, median (range)	71 (45-221)	383 (251-928)	<0.001*	57 (38-110)	374 (247-847)	282 (122-584.5)	<0.001*
Sedimentation, median (range)	30 (20-51)	78 (53-97)	<0.001*	26 (17-39)	75.5 (51-95)	64 (36-88)	<0.001*
CRP, median (range)	12.5 (4.8-41)	80 (31.9-152)	<0.001*	9.4 (4.6-21)	69.3 (31.8-149)	45 (12.9-121)	<0.001*
Procalcitonin, median (range)	0.2 (0.1-0.4)	0.2 (0.1-0.7)	0.321	0.2 (0.1-1.1)	0.2 (0.1-0.6)	0.2 (0.1-0.7)	0.636
Fibrinogen, median (range)	230 (135-348)	413 (354-497)	<0.001*	185 (119-278)	411.5 (348-497)	387 (289-467)	<0.001*
LDH, median (range)	300.5 (217-335)	331 (253-449)	0.012*	300 (224-310)	327 (253-447)	310 (246-403)	0.008*
NLR, mean (range)	6.1 (4.4-10.2)	8.2 (5.1-14.9)	0.047*	5.8 (4.1-10.2)	9.1 (6.8-14.9)	7.1 (4.7-11.7)	0.003*
SII, mean (range)	1368 (733-2486)	2014 (1204-3123)	0.032*	1389 (731-2331)	2495 (1348-3172)	1530 (918-2749)	0.002*

*p<0.05
CRP: C-reactive Protein, NLR: neutrophil/lymphocyte ratio, SII: Systemic immune-inflammation index, LDH: Lactate dehydrogenase, WBC: White Blood Cell

Table 2. The association between BDI, and BAI levels, and inflammatory parameters in patients with depression or anxiety

	BDI		BAI	
	r	p	r	p
WBC	-0.065	0.592	0.068	0.545
Neutrophil	-0.052	0.665	0.106	0.345
Lymphocyte	0.143	0.235	0.039	0.725
Platelet	-0.087	0.472	0.131	0.242
D-Dimer	-0.059	0.622	-0.026	0.819
Ferritin	-0.002	0.987	0.24	0.035*
Sedimentation	0.072	0.552	0.156	0.163
CRP	0.034	0.775	0.168	0.13
Procalcitonin	-0.03	0.807	0.136	0.224
Fibrinogen	0.075	0.534	0.178	0.11
LDH	0.113	0.348	0.035	0.755
NLR	-0.079	0.514	0.09	0.42
SII	-0.11	0.363	0.111	0.322

*p<0.05
BDI: Beck Depression Inventory, CRP: C-reactive Protein, SSI: Systemic immune-inflammation index, WBC: White Blood Cell, r: correlation coefficiennts, Spearman test was used, BAI: Beck Anxiety Inventor, NLR: neutrophil/lymphocyte ratio, LDH: Lactate dehydrogenase

inflammatory parameters in patients with anxiety. Congruently, there was no significant association between inflammatory markers and BDI scores in patients with depression.

The respiratory epithelium is the primary target of coronaviruses. The target receptor for binding to the cell and subsequent internalization is realized by the angiotensin-converting enzyme 2 receptor (ACE-2). ACE-2 is effective in the regulation of blood pressure and is also present in the nervous system. COVID-19 has been reported to lead to blood-brain barrier disruption due to endothelial dysfunction and, as a result, to neuropsychiatric findings due to direct or indirect mechanisms (16).

The aetiology of the psychiatric consequences of infection with COVID-19 is likely to be multifactorial and might include the direct effects of viral infection (including brain infection), cerebrovascular disease (including the context of a procoagulant state), the degree of physiological compromise (e.g., hypoxia), the immunological response, medical interventions, social isolation, the psychological impact of a novel severe and potentially fatal illness, concerns about infecting others, and stigma. The immune response in SARS-CoV-2 infection is of interest. There might be a hyperinflammatory state similar to that seen in haemophagocytic lymphohistiocytosis in which there are increased concentrations of C-reactive protein, ferritin, and interleukin-6. However, this state is likely to be short lived (17).

Neuroinflammation, blood-brain barrier disruption, peripheral immune cell invasion into the CNS, neurotransmission impairment, hypothalamic-pituitary-adrenal axis dysfunction, microglial activation, and indoleamine 2.3-dioxygenase (IDO) induction, all represent interaction pathways between immune systems and psychopathological mechanism underpinning psychiatric disorders (18–20).

The SII is an objective marker of the balance between host systemic inflammation and immune response status considering neutrophils, platelets, and lymphocytes involved in different pathways of immune/inflammatory response (21). In a single study, higher SII levels were associated with major depressive disorder (22).

Only one study in the literature analyzed the relationship between inflammatory markers and the levels of depression and anxiety in patients with COVID-19. In this study, in which 402 COVID-19 survivors were evaluated after one month from hospital discharge, baseline NLR and SII scores were positively correlated with the levels of depression and anxiety (23). Correlatively in our study, baseline NLR and SII scores were positively correlated with the levels of depression and anxiety on the 15th day of follow-up after discharge from the hospital.

In the light of the studies discussed above, it is predicted that high levels of inflammatory biomarkers might play a role in the pathogenesis of the psychiatric disorders secondary to COVID-19 as well as mood disorders (24). Besides, this approach can lead to new researches analyzing specific targets for treating inflammation-associated neuropsychiatric disorders (25).

We consider that social isolation, inability to see the relatives, concerns of death, and disability, concerns about the disease process, and stigmatisation following hospital discharge might contribute to the high levels of anxiety and depression in patients with COVID-19.

Female gender was determined as a risk factor for the occurrence of psychopathological disorders related to COVID-19 in the previous epidemiological studies (23, 26, 27). Moreover, younger patients showed higher levels of anxiety disorders, depression, and sleep disturbances, in agreement with previous studies describing a worse psychological impact of the COVID-19 pandemic in younger people (23, 28). In line with the previous studies, depression and anxiety levels were also higher in young and female patients in our study.

The self-rating inventories are among the limitations of our study. However, the same researcher performed all psychiatric interviews and examined them at an early stage. Secondly, the low number of patients can be considered as the another limitation of our study. On the other hand, inclusion of only the PCR-positive patients, and exclusion of the suspected PCR-negative cases might be the reason for the low number of patients. Thirdly, this was a cross-sectional study. Thus long-term psychiatric effects that can be seen in the patients could not be evaluated.

In conclusion, COVID-19 primarily affects the respiratory and cardiovascular systems. Nonetheless, psychiatric involvement is not uncommon and can lead to severe problems if not detected and managed early. It is recommended that clinicians should be vigilant regarding psychiatric involvement in COVID-19 patients presenting with high inflammatory parameters. Thus, further studies are needed to evaluate this relationship more thoroughly.

Ethics Committee Approval: Ethics Committee of Sakarya Training and Research Hospital approved the study (Date: 11.09.2021, Number: 01-24T14-5036).

Informed Consent: Informed consent from all the participants were obtained.

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